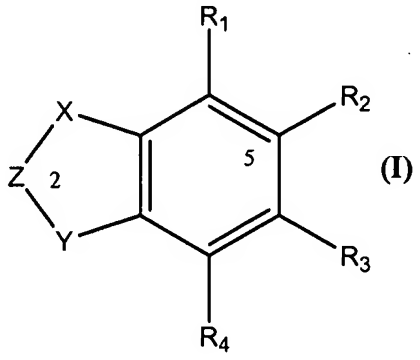
Claims Listing

1. (Currently amended) A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt ~~or prodrug~~ thereof



(I)

wherein

X is ~~selected from O , S , C(R5)(R5') or N(R6)~~;

Y is ~~selected from N(R7) , O , S or C(R7)2~~;

Z is ~~selected from C(O) , C(S) , C(=NR6) , S(O) or S(O)2~~;

R_1 is selected from hydrogen, or ~~C_{1-3}alkyl, $(CR_5R_{5'})_nOR_7$, $(CR_5R_{5'})_nSR_7$, $(CR_5R_{5'})_nN(R_6)_2$ and~~ $(CR_5R_{5'})_n$halo;

R_2 is selected from the group consisting of C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mC(O)R_8$, $(CR_{12}R_{12'})_mC(S)R_8$, $(CR_{12}R_{12'})_mS(O)R_8$, $(CR_{12}R_{12'})_mS(O)_2R_8$, $(CR_{12}R_{12'})_mOR_9$, $(CR_{12}R_{12'})_mSR_9$, $(CR_{12}R_{12'})_nNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ and $(CR_{12}R_{12'})_mR_{13}$;

R_3 is selected from hydrogen, C_1-C_6alkyl, $(CR_{16}R_{16'})_pNR_{14}R_{15}$, $(CR_{16}R_{16'})_pOR_{17}$, ~~$(CR_{16}R_{16'})_pSR_{17}$~~, $(CR_{16}R_{16'})_p$halo, and $(CR_{16}R_{16'})_pNO_2$, ~~$(CR_{16}R_{16'})_nC(O)R_{28}$~~,

~~$(CR_{16}R_{16'})_nC(=NR_{24})R_{22}$, $(CR_{16}R_{16'})_nS(O)R_{17}$, $(CR_{16}R_{16'})_nS(O)_2R_{17}$, $(CR_{16}R_{16'})_nS(O)_3R_{17}$ and $(CR_{16}R_{16'})_pC(R_{18})_3$~~;

R_4 is ~~selected from~~ hydrogen, or halogen ~~C_1-C_3alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl and $(CR_{12}R_{2'})_nC(R_{18})_3$~~;

Each R_5 and R_5 is independently ~~selected from~~ hydrogen, ~~C_1-C_3alkyl, halo, OR_7, SR_7 and $N(R_6)_2$~~;

~~Each~~ R_6 is ~~independently selected from~~ hydrogen, or C_1-C_3alkyl ~~and OR_7~~;

~~Each~~ R_7 is ~~independently selected from~~ hydrogen ~~and~~ or C_1-C_3alkyl;

R_8 is selected from the group consisting of hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, OR_{19}, SR_{19}, $N(R_{20})_2$, $[NH—CH(R_{21})—C(O)]_q—OR_{29}$, ~~[sugar]$_q$~~ pyranosyl and $(CR_{12}R_{12'})_tR_{13}$;

R_9 is ~~selected from~~ hydrogen, ~~C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_tR_3$, $C(O)R_{23}$, CO_2R_{23}, $C(S)R_{23}$, $C(S)OR_{23}$, $S(O)R_{23}$, $S(O)_2R_{23}$, $[C(O)CH(R_{21})NH]_q—R_{23}$ and [sugar]$_q$~~;

R_{10} and R_{11} are independently selected from hydrogen, ~~C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mR_{13}$~~; and $C(O)R_{23}$, ~~$C(S)R_{23}$, $S(O)R_{23}$, $S(O)_2R_{23}$, $[C(O)CH(R_{21})NH]_q—R_{23}$, [sugar]$_q$ and $NHC(=NR_{25})—NH_2$~~;

Each R_{12} and $R_{12'}$ is independently ~~selected from~~ hydrogen, ~~C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, OR_{24}, SR_{24}, halo, $N(R_{24})_2$, CO_2R_{24}, CN, NO_2, aryl or heterocyclyl~~;

R_{13} is selected from OR_{25}, SR_{25}, halo, $N(R_{25})_2$, and $C(O)R_{31}$, ~~CN, $C(R_{18})_3$, aryl or heterocyclyl~~;

R_{14} and R_{15} are ~~independently selected from~~ each hydrogen, ~~C_1-C_3alkyl, OR_{17}, $(CR_{16}R_{16'})_pC(R_{18})_3$~~;

Each R_{16} and $R_{16'}$ is ~~independently selected from~~ hydrogen~~, C_1-C_3alkyl, halo, OR_{17}, SR_{17} and $N(R_{17})_2$~~;

~~Each~~ R_{17} is ~~independently selected from~~ hydrogen ~~and C_1-C_3alkyl;~~

~~Each R_{18} is independently selected from hydrogen and halo~~;

R_{19} and each R_{20} are independently selected from hydrogen, C_1-C_{20}alkyl, ~~C_2-C_{20}alkenyl, C_2-C_{20}alkynyl~~ and, $(CR_{26}R_{26'})_tR_{27}$;

R_{21} is the characterising group of an amino acid wherein the amino acid is alanine, phenylalanine, serine, homoserine or norvaline;

R_{22} is ~~selected from C_1-C_6alkyl, NH_2,~~ $NH(C_{1\text{-}6}alkyl)$~~, $N(C_{1\text{-}6}alkyl)_2$, OR_{29} or SR_{29}~~;

R_{23} is ~~selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, aryl~~ $(CR_{26}R_{26'})_tR_{27}$;

Each R_{24} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{25} is independently selected from hydrogen, and C_1-C_6alkyl, ~~$C_{1\text{-}3}$alkoxy$C_{1\text{-}3}$alkyl, aryl and heterocyclyl~~;

Each R_{26} and $R_{26'}$ is independently ~~selected from~~ hydrogen, ~~C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, OR_{29}, SR_{29}, halo, $N(R_{29})_2$, CO_2R_{29}, CN, NO_2, aryl and heterocyclyl~~;

R_{27} is selected from ~~hydrogen~~, OR_{30}, SR_{30}, ~~halo, $N(R_{30})_2$, CO_2R_{30},~~ and aryl ~~and heterocyclyl;~~

~~R_{28} is selected from hydrogen, $C_{1\text{-}6}$alkyl, OR_{29}, SR_{29} or $N(R_{29})_2$~~;

Each R_{29} is independently selected from hydrogen and C_1-C_3alkyl;

Each R_{30} is independently selected from ~~hydrogen~~, C_1-C_3alkyl, ~~aryl~~ and heterocyclyl;

R_{31} is ~~selected from C_{1-3}alkyl, OH, C_{1-3}alkoxy, aryl, aryloxy, heterocyclyl and~~ heterocyclyloxy;

n is 0 or an integer from 1 to 3;

m is 0 or an integer from 1 to 20;

p is 0 or an integer from 1 to 6;

q is an integer from 1 to 5;

t is an integer from 1 to 10;

wherein alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

2. (Currently amended) A method according to claim 1 wherein X is ~~selected from the group consisting of —N(H)—, —N(C_{1-3}alkyl)—, —N(OH)—, —N(OC_{1-3}alkyl)—, —O—, —S—, —CH_2—, —CH(OH)—, —CH(NH_2)—, —CH(C_{1-3}alkyl)—, —CH(halo)—, —CH(SH)—, —CH(OC_{1-3}alkyl), —CH(SC_{1-3}alkyl)~~ Y is —N(H)—, and Z is —C(O)—.

Claims 3 - 17 (Cancelled)

18. (Original) A method according to claim 1 wherein the compound of formula 1 is selected from the group consisting of: benzimidazole-2-one-5-n-pentanoate, 5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate, benzimidazole-2-one-5-methanoate, benzimidazole-2-one-5-ethanoate, 3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-benzimidazole-2-one-5-carboxylate, 5-bromo-6-methylbenzimidazol-2-one, 5-hydroxy-6-methylbenzimidazol-2-one, 5-dodecanylbenzoimidazol-2-one, 4,5,7-tribromo-6-

methylbenzimidazol-2-one, 4,5,6,7-tetrabromobenzimidazol-2-one, 5-methyl-6-nitrobenzimidazol-2-one, 5-amino-6-methylbenzimidazol-2-one, N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide, pentyl-benzimidazol-2-one-5-carbothioate, 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid, 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester, 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide, N-butyl-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboximidamide, 5-heptanoylbenzofuran-2(3H)-one, methyl 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoate, 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoic acid, methyl 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoate, 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoic acid, and N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboxamide.

19. (Currently amended) A method of treating, preventing or diagnosing a disease or condition wherein MIF cytokine or biological activity is implicated comprising the administration of a treatment, prevention or diagnostic effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ thereof to a subject in need thereof.

20. (Original) A method according to claim 19 wherein the disease or condition is selected from autoimmune diseases, solid or haemopoitic tumours and chronic or acute inflammatory diseases.

21. (Currently amended) A method according to claim 19 wherein the disease or condition is selected from the group consisting of Rheumatic diseases, ~~spondyloarthropathies, crystal arthropathies, Lyme disease,~~ connective tissue diseases, ~~vasculitides,~~ glomerulonephritis, ~~interstitial nephritis,~~ inflammatory bowel disease, ~~peptic ulceration, gastritis, oesophagitis,~~ liver disease, ~~autoimmune diseases, pulmonary diseases,~~ cancers whether primary or metastatic, atherosclerosis, ~~disorders of the hypothalamic-pituitary-adrenal axis, brain disorders, corneal disease, iritis,~~ iridocyclitis, ~~cataracts,~~ uveitis, sarcoidosis, ~~diseases characterised by modified angiogenesis, endometrial function,~~ psoriasis, endotoxic (septic) shock, exotoxic (septic) shock, infective (true septic) shock, ~~other complications of infection, pelvic inflammatory disease,~~ transplant rejection, ~~allergies, allergic rhinitis,~~ bone diseases, ~~atopic dermatitis, UV(B)-induced dermal cell activation, malarial complications,~~ diabetes mellitus, ~~pain, inflammatory consequences of trauma or ischaemia, testicular dysfunctions~~ and wound healing.

22. (Currently amended) A method according to claim 21 wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ~~ankylosing spondylitis,~~ reactive arthritis, ~~Reiter's syndrome, gout, pseudogout, calcium pyrophosphate deposition disease,~~ systemic lupus erythematosus, systemic sclerosis, ~~polymyositis, dermatomyositis, Sjögren's syndrome, polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome,~~ ulcerative colitis, Crohn's disease, ~~cirrhosis,~~ hepatitis, ~~diabetes mellitus, thyroiditis, myasthenia gravis, sclerosing cholangitis, primary biliary cirrhosis, diffuse interstitial lung diseases, pneumoconioses, fibrosing alveolitis,~~ asthma, ~~bronchitis, bronchiectasis, chronic obstructive pulmonary disease,~~ adult respiratory distress syndrome, colon cancer, lymphoma, lung cancer, melanoma, prostate cancer, breast cancer, stomach cancer,

~~leukemia, cervical cancer and metastatic cancer, ischaemic heart disease,~~ myocardial infarction, ~~stroke, peripheral vascular disease, Alzheimer's disease,~~ multiple sclerosis, diabetic retinopathy, ~~parturition, endometriosis,~~ osteoporosis, ~~Paget's disease, sunburn~~ and skin cancer.

23. (Original) A method of claim 19 wherein the subject is a human subject.

Claims 24-25. (cancelled)

26. (Currently amended) A method of treating or preventing a disease or condition wherein MIF cytokine or biological activity is implicated comprising: administering to a mammal a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ thereof and a second therapeutic agent.

27. (original) A method according to claim 26 wherein the second therapeutic agent is a glucocorticoid.

28. (Currently amended) A method of prophylaxis or treatment of a disease or condition for which treatment with a glucocorticoid is indicated, said method comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ thereof.

29. (Currently amended) A method of treating a steroid-resistant disease or condition comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as

defined in claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ thereof.

30. (Currently amended) A method of enhancing the effect of a glucocorticoid in mammals comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ thereof simultaneously, separately or sequentially with said glucocorticoid.

Claims 31-40. (Cancelled)

41. (New) A method according to claim 1 wherein

R_1 is hydrogen or $(CR_5R_{5'})_n$halo;

R_2 is selected from C_{1-20}alkyl, $(CR_{12}R_{12'})_mC(O)R_8$, $(CR_{12}R_{12'})_mS(O)_2R_8$, $(CR_{12}R_{12'})_nNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ and $(CR_{12}R_{12'})_mR_{13}$;

R_3 is selected from hydrogen, C_{1-6}alkyl, $(CR_{16}R_{16'})_pNR_{14}R_{15}$, $(CR_{16}R_{16'})_pOR_{17}$, $(CR_{16}R_{16'})_p$halo and $(CR_{16}R_{16'})_pNO_2$;

R_4 is hydrogen or halogen;

Each R_5 and $R_{5'}$ is independently hydrogen;

R_8 is selected from C_1-C_{20}alkyl, OR_{19}, SR_{19}, $N(R_{20})_2$, $[NH\text{-}CH(R_{21})\text{-}C(O)]_q\text{-}OR_{29}$, pyranosyl and $(CR_{12}R_{12'})R_{13}$;

R_9 is hydrogen;

R_{10} and R_{11} are independently selected from hydrogen and $C(O)R_{23}$;

Each R_{12} and $R_{12'}$ is independently hydrogen;

R_{13} is selected from OR_{25}, SR_{25}, halo, $N(R_{25})_2$ and $C(O)R_{31}$;

R_{14} and R_{15} are each hydrogen;

Each R_{16} and $R_{16'}$ is hydrogen;

R_{17} is hydrogen;

R_{19} and each R_{20} are independently selected from hydrogen, C_1-C_{20}alkyl, and $(CR_{26}R_{26'})_tR_{27}$;

R_{21} is the characterising group of phenylalanine or serine;

R_{22} is $NH(C_{1-6}alkyl)$;

R_{23} is $(CR_{26}R_{26'})_tR_{27}$;

Each R_{24} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{25} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{26} and $R_{26'}$ is independently hydrogen;

R_{27} is selected from OR_{30}, SR_{30} and aryl;

Each R_{29} is independently selected from C_1-C_3alkyl and heterocyclyl; and

R_{31} is heterocyclyloxy.

42. (New) A method according to claim 41 wherein

n is 0;

m is 0;

p is 0;

q is 0; and

t is 1 or 2.

43. (New) A method according to claim 1 wherein the compound of formula (I) is benzimidazole-2-one-5-n-pentanoate.